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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/995,225	11/26/2001	Ruoping Chen	AREN-0308	1454

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EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/995,225	**Applicant(s)** CHEN ET AL.	
	Examiner Nirmal S. Basi	**Art Unit** 1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 22 December 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *22 December 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): 35USC 112, second paragraph rejection of claims 41-43 and 46-56.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *29 and 41-61*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). 5/10/05, 12/6/04
13. ☒ Other: attached PTO892.

Continuation of 11. does NOT place the application in condition for allowance because: Applicant has not overcome the rejections under 35USC101 and 112 first paragraph, of record in the Office Action mailed 7/28/05. The rejections under 35USC101 and 112 first paragraph, of record in the Office Action mailed 7/28/05 are maintained. Applicants arguments filed 12/22/05 are discussed below.

Applicants argue:
a) hRUP35 has utility for use in methods of identifying materials, which bind hRUP35 and treat sensorimotor processing and arousal disorders, i.e. screening methods,
b) method of identifying materials which bind to a specific receptor is a method that is not applicable to the general class of receptors,
c) hRUP35 can be used to treat sensorimotor processing and arousal disorders, applicants specifically refer to paragraph 0075 and paragraph 0214 following table E for support,
d) hRUP35 is expressed in the thalamus, proteins located/expressed in the thalamus are associated with sensorimotor processing arousal or disorders thereof, hRUP35 expression results in increased IP3 in thalamus,
e) GPCR expression in thalamus can modulate sensorimotor processing arousal in the thalamus and in support of this statement write, "Applicants submit herewith a copy of Salt and Eaton, Neurochem. Int (1994) 24:451-458, which teaches that a GPCR known to stimulate IP3 metabolism modulates sensory response in thalamus, e.g. response evoked by noxious thermal stimulation of the peripheral receptive field (see, e.g. p. 455, lines 1-28 of the Discussion.) This teaching is further supported by Miyata et al., J Neurosci (2003) 23:8098-8108 (also submitted herewith). These references support the credibility of Applicants' utility, and make it more likely than not that one skilled in the art would not have questioned Applicants' asserted utility."
f) the specification associates sensorimotor processing and arousal with hRUP35 through its expression in the thalamus and those of skill in the art would appreciate that hRUP35's expression in the thalamus and accompanying increase in intracellular IP3 would make it useful in treatment of diseases/disorders of the thalamus such as sensorimotor processing and arousal disorders,
g) knowledge of the natural ligand for hRUP35 is not requirement for utility, applicants argue using niacin receptor as support.
Under written description Applicants argue they are claiming only those polynucleotides amplifiable by RT-PCR employing the specific claimed primers and thus Applicants assert that those of skill in the art would readily appreciate that Applicants were in possession of the invention.

It is noted that Applicant has not provided copies of the references by Salt and Eaton, Neurochem. Int (1994) 24:451-458, and Miyata et al., J Neurosci (2003) 23:8098-8108, said references have not been considered.

35USC101 and 112 first paragraph issues:

Applicant's arguments have been fully considered but are not found persuasive, for the reasons given below and for those of record. First, examiner is not disputing Applicants assertion that hRUP35 expression in the thalamus results in increased levels of IP3. The assertion that hRUP35 can be used to treat sensorimotor processing and arousal disorders is taken from a laundry list of disorders following Table E, which applicant's use for support. Following Table E, the specification discloses, "Diseases and disorders related to receptors located in these tissues or regions include, but are not limited to, cardiac disorders and diseases (e.g. thrombosis, myocardial infarction; atherosclerosis; cardiomyopathie); kidney disease/disorders (e.g. renal failure; renal tubular acidosis, renal glycosuria; nephrogenic diabetes insipidus; cystinuria; polycystic kidney disease); eosinophilia; leukocytosis; leukopenia; ovarian cancer; sexual dysfunction; polycystic ovarian syndrome; pancreatitis and pancreatic cancer; irritable bowel syndrome; colon cancer; Crohn's disease; ulcerative colitis; diverticulitis; Chronic Obstructive Pulmonary Disease (COPD); Cystic Fibrosis; pneumonia; pulmonary hypertension; tuberculosis and lung cancer; Parkinson's disease; movement disorders and ataxias; learning and memory disorders', eating disorders (e.g., anorexia; bulimia, etc.),' obesity; cancers; thyme; myasthenia gravis; circulatory disorders', prostate cancer; prostitutes; kidney disease/disorders (e.g., renal failure; renal tubular acidosis', renal glycosuria; nephrogenic diabetes insipidus; cystinuria; polycystic kidney disease); sensorimotor processing and arousal disorders; obsessive-compulsive disorders; testicular cancer; pianism; prostates; hernia; endocrine disorders; sexual dysfunction; allergies; depression; psychotic disorders; migraine; reflux; schizophrenia; ulcers; bronchospasm; epilepsy; prostatic hypertrophy; anxiety; rhinitis; angina; and glaucoma. Accordingly, the methods of the present invention may also be useful in the diagnosis and/or treatment of these and other diseases and disorders."
Therefore, the laundry list of possibly dysfunctions associated with claimed invention includes all diseases known to man. Applicant is fishing for a function or dysfunction related to claimed polynucleotide. The presence of expression of hRUP35 in the thalamus and its associated ability to increase IP3 levels in isolated IP3 cells does not support the claimed utility.

The ability of hRUP35 to increase IP3 levels in the cell type "293 cells" does not mean it will evoke the noxious thermal stimulation of the peripheral receptive field by the GPCR in Applicants response. Further it is not clear what is the relationship of hRUP35 to noxious thermal stimulation of the peripheral receptive field and how it further relates to a specific sensorimotor processing and arousal disorder. Even if a GPCR (with known function) increases IP3 (an example of a second messenger) levels in a specific cell the art discloses that another receptor which also affects IP3 levels may have a completely different biological function. Cells are exposed to may extracellular stimuli, yet they respond appropriately only to specific signals, often by means of just a handful of intracellular messengers. There is more to specificity than the controlled expression of signaling proteins. Taylor (Calcium signaling:IP3 rises... and again, Current Biology, Vol. 11:R352-R353, 2001), discusses these issues at length and states," Even within a single cell, different receptors may use the same intracellular messenger molecule to very different effect", page R352. The ability of GPCRs to interact with other proteins in the cell and the effect of feedback mechanisms allow them to use the same Gq proteins or second messenger pathways but have very different effects. For example, Taylor (page R352, column 2) discloses that in pancreatic acinar cells cholecytokinin and acetylcholine receptors use the same Gq proteins to stimulate phospholipase C and so trigger Ca2+ release from intracellular stores, yet the patterns of Ca2+ signals they evoke are quite different". Such diversity sits uneasily with mechanisms wholly dependent on Ca2+ regulation of IP3

receptors. The diversity of signal transduction also applies to receptor subtypes. For example, stimulation of one subtype of metabotropic glumate receptor, mGluR5, evokes Ca2+ spikes via IP3, but stimulation of another subtype expressed in the same cell, mGluR1 depends upon a single Ca2+ transient. The difference depends upon a single PKC phosphorylation site in mGgluR5 (see Taylor, page R354, column 1). The versatility of the signaling mechanism in cells is also discussed by Berridge et al (Berridge et al, The versatility and universality of calcium signaling, Nature Reviews Molecular Cell Biology, Vol. Pages 11-21, 2000). Berridge discloses the versatility of the signaling mechanism is enhanced by having different second messenger mobilizing molecules linked to separate input signals. Therefore in a given cell two separate molecules linked to the same second messenger such as IP3 can have different effects on the cell.

Although the claimed receptor was isolated in the thalamus there is no disclosure in the specification that hRUP35 is associated with a specific sensorimotor processing or arousal disorder, nor can one be determined on the specification or prior art. There is no disclosure of the specific sensorimotor processing or arousal disorder associated with hRUP35 function or dysfunction. Sensorimotor processing disorders include tremor disorders, action tremor disorders, and disorders of impaired motor coordination, and that arousal disorders include impaired cognitive performance. Although the claimed receptor has been shown to be expressed in the thalamus there is no disclosure of the specific association with a sensorimotor processing or arousal disorder. The determination of the specific association with a sensorimotor processing or arousal disorder requires further research. For example, does the increased expression of hRUP35 cause tremor disorders, action tremor disorders, arousal disorders etc.? Does the decreased expression of hRUP35 cause tremor disorders, action tremor disorders, arousal disorders etc.? Are agonists beneficial for treatment or are antagonists beneficial? Is the claimed invention the normal gene product or the dysfunctional gene product. Does the claimed polynucleotide affect sensorimotor processing or arousal disorder? What is the specific disorder? The examiner can find no answers to these question in the specification. Unlike the argued agonists of the niacin receptor no agonists or antagonists of RUP35 are disclosed which can be used to support a specific, substantial and credible utility. Again the determination of said ligands and their specific use requires further research. Unlike the niacin receptor agonist which can be used to raise HDL levels in man no agonists or antagonists are disclosed for RUP35 which have a specific use such as raising HDL levels. When the claimed GPCR is compared to Example 12 of Revised Interim Utility Guidelines Training Materials said GPCR has no specific disclosed function or specific ligands that can be used to support utility. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed hRUP35 further experimentation is necessary to attribute a utility to the claimed hRUP35. The instant application does not disclose the biological role of hRUP35 or its significance. The utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the hRUP35 of the instant invention. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, a specific and substantial credible utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, applicants claimed invention is incomplete.

Thus the corresponding asserted utilities are essentially methods of using hRUP35 to identify disease states associated with hRUP35 dysfunction, as targets for drug discovery or further research upon itself. Therefore the asserted utilities are essentially methods of testing for or for potentially treating unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. Treating or testing for compounds that interact with hRUP35 which may be implicated in an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed hRUP35 further experimentation is necessary to attribute a utility to the claimed polypeptides and fragments thereof. See Brenner v. Manson, 383 U.S. 519, 535□36, 148 USPQ 689, 696 (1966) (noting that Congress intended that no patent be granted on a chemical compound whose sole utility consists of its potential role as an object of use testing, and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

As discussed in the prior Office Action the family of proteins related to hRUP35 may have diverse effects and bind a diverse number of ligands. The family of proteins having GPCR like domains has different levels of expression, and play roles in the pathogenesis of various diseases. Although the family of receptor proteins having GPCR like domains may share some common structural motifs, various members of the family may have different sites of action and different biological effects. In the absence of knowledge of the ligand for hRUP35 or the biological significance of these proteins, there is no immediately evident patentable use. To employ a protein of the instant invention in any of the disclosed methods would clearly be using it as the object of further research. Such a use has been determined by the courts to be a utility which, alone, does not support patentability. Since the instant specification does not disclose a credible real world use for hRUP35 then the claimed invention as disclosed does not meet the requirements of 35 U.S.C.101 as being useful.

hRUP35 belongs is a family in which the members have divergent functions. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family.

The diversity of the biochemical function and the wide range of regulatory pathways involving GTP-binding proteins are well known in the art. Without some common biological activity for the family members, a new member would not have a specific, substantial, or credible utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different biological activities which may be related to tissue distribution but there is no evidence that the claimed compounds share any one of diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for screening assays or diagnosis is to argue a general, nonspecific utility that would apply to virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use. Further, the specification does not disclose the significance of any test results, nor is there any evidence that the significance was known as of the filing date. If the expression of the claimed hRUP35 increases, is this a positive or negative outcome? Would this be a toxic response or not? The disclosure is insufficient

to evaluate the results of the test in any meaningful manner.

Written Description Issues

Pertaining to written description, Applicants were in possession of one subtype of hRUP35 (polynucleotide of SEQ ID NO:15 encoding the polypeptide of SEQ ID NO:16), other subtypes were neither isolated or even known to exist. Applicant has not disclosed the other subtypes of hRUP35 that may exist in the thalamus but only a way to find related molecules using PCR. Even if other subtypes of hRUP35 do exist their physiological function may be unrelated, just as mGluR5 differs from mGluR1 (see above). The limitation that the GPCR be expressed in the thalamus and increase IP3 level is insufficient to overcome the lack of knowledge of the physiological function or ligand for hRUP35. The claimed hRUP35 has not been shown to be involved in a specific disorder, only postulated based on a laundry list of dysfunctions. Even if variants of hRUP35 are found would they have the same biological function as hRUP35? There are no ways to test based on the lack of knowledge of the biological function of the variants. As disclosed above the knowledge of the second messenger may be insufficient to predict biological function. The variants encompassed by claims 44-61 may be unrelated structurally and in their physiological function to hRUP35. The primers (SEQ ID NO:41 and 42) used to isolate the polynucleotide are 27 and 25 nucleotides in length. The polynucleotide of SEQ ID NO:15 is 1062 nucleotides in length. What are the variants that will be isolated using said primers and what will be their biological function? Apart from the known sequence of primers the PCR method will isolate an unpredictable sequence of polynucleotide; based on SEQ ID NO:15 this may be more than 1000 nucleotides in length. This encompasses trillions of variants to test. Does the applicant know how to make any one of these that will have the ligand binding properties of hRUP35? The specification does not disclose any such variants. As discussed above the structure of a GPCR in addition to its signaling mechanism, in this case IP3, determines it ability to exert its biological function. As in the case of mGluR5 a single phosphorylation site in the molecule evokes a different effect from its related subtype, mGluR1. In instant case the PCR method may isolate a species of GPCR that is found in the thalamus and increases IP3 levels but be unrelated in its physiological function to hRUP35.

The skilled artisan cannot envision the detailed chemical structure of the encompassed compounds and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid or polypeptide is itself is required. See Fibers v. Revel, 25 USPQ d. 1601 at 1606 (CAFC 1993) and Amen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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